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Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

VIA COURIER

Amendment to Citizen Petition
Docket Number 02P-0406/CP1
Inclusion of Pediatric Waiver Request

Dear Sir or Madam:

The petition cited above was submitted on September 10, 2002. The petition requested the Commissioner of the Food and Drug Administration to declare that the drug product **Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension 200 mg/28.5 mg, 400 mg/57 mg and 600 mg/42.9 mg** is suitable for submission as an Abbreviated New Drug Application (ANDA).

In December of 2003, Congress passed the Pediatric Research Equity Act (PREA) of 2003 that amended the Federal Food, Drug and Cosmetic Act (The Act) to provide the Agency authority to require drug firms to study certain drugs in pediatric patients, if the Agency felt that such study would provide beneficial health data for that patient population. This letter is based on the requirements outlined in PREA and references the Draft Guidance for Industry [Recommendations for Complying with the Pediatric Rule (21 CFR 314.55(a) and 601.27(a)), dated November 2000].

Reference is also made to the Agency's communication dated February 3, 2004, recommending submission of a waiver with supporting information and documentation in accordance with the provisions of Section 2 of PREA as an amendment to the suitability petition.

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Section 505B(a)(4)(A)(iii) of The Act (as amended by PREA) provides a provision for a waiver from such requirement if:

> (iii) the drug or biological product --
>
> > (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and
> >
> > (II) is not likely to be used in a substantial number of pediatric patients.

The petitioner hereby requests that a waiver from the conduct of pediatric studies for all age groups be granted for this petition.

The Reference Listed Drugs Augmentin®/Augmentin ES-600™ Powder for Oral Suspension[1] (GlaxoSmithKline) are currently available in a powder for oral suspension and are, according to the approved labeling, recommended for use in the treatment of infections caused by susceptible strains of certain organisms in conditions such as lower respiratory tract infections and otitis media.

The petitioner's proposed product, Tablets for Oral Suspension, forms an oral suspension on dispersion similar to the Reference Listed Drug. This petition requests a change in dosage form from "Powder for Oral Suspension" to "Tablets for Oral Suspension." The final dosage form consumed by the patient is the "suspension" and is identical for both the petitioner's product and the Reference Listed Drug.

The proposed product, Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension,[2] is designed to provide patients a more convenient dosage form of amoxicillin and clavulanate potassium with respect to unit-dose dispensing, ease of administration to patients who have difficulty swallowing, and storage and administration (for example, during travel). These benefits, while not excluding pediatrics, are directed to the adult population. The petitioner believes that Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension[2] does not represent a meaningful therapeutic benefit over existing antibiotic therapies or over the Reference Listed Drugs, Augmentin®/Augmentin ES-600™ Powder for Oral Suspension,[1] for the pediatric patient population.

Furthermore, the petitioner believes that additional clinical studies in the pediatric population with the petitioner's tablets for oral suspension would not offer meaningful data, nor would they demonstrate a therapeutic benefit over Augmentin®/Augmentin ES-600™ Powder for

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[1] The Reference Listed Drugs include: Augmentin® (200 mg amoxicillin and 28.5 mg clavulanate potassium/5 mL; 400 mg amoxicillin and 57 mg clavulanate potassium/5 mL) and Augmentin ES-600™ (600 mg amoxicillin and 42.9 mg clavulanate potassium/5 mL). Augmentin ES-600™ is specified as the Reference Listed Drug.

[2] The Petitioner's proposed products are Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension (200 mg amoxicillin and 28.5 mg clavulanate potassium; 400 mg amoxicillin and 57 mg clavulanate potassium; and 600 mg amoxicillin and 42.9 mg clavulanate potassium.

Oral Suspension[1] in the pediatric patient population for which it is indicated. As stated in the product labeling for both Augmentin® and Augmentin ES-600™ Powder for Oral Suspension,[1] pediatric studies have been conducted with the Reference Listed Drug (Augmentin ES-600™) and with the other lower strength Augmentin® formulations, and the product labeling contains adequate dosing and administration information for the pediatric population. The label for Augmentin® Powder for Oral Suspension specifies doses for the pediatric population from neonates to 3 months of age, and for 3 months and older:

> Neonates and infants aged < 3 months: Recommended dose is 30 mg/kg/day amoxicillin divided into two doses.
>
> Children 3 months and older: Dosage varies with infection type. For otitis media, the recommended dose is 45 mg/kg/day divided into two doses. For less severe infections, the recommended dose is 25 mg/kg/day divided into two doses.

The planned labeling for Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension (200 mg amoxicillin and 28.5 mg clavulanate potassium; 400 mg amoxicillin and 57 mg clavulanate potassium) will be very similar in providing dose information for the allowable weight groups:

> Neonates and infants aged < 3 months: Dosage is 30 mg/kg/day amoxicillin divided in two doses. Since neonates and infants <3 months do not usually reach a body weight of 13 kg, it is highly unlikely that this age group will receive Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension.
>
> Children 3 months and older: Dosage varies with infection type: For otitis media, administer 45 mg/kg/day divided in two doses. For a child of approximately 9 kg, suspend and have the child drink one-200 mg tablet in water every 12 hours (see Table 1 below). For other infections, administer 25 mg/kg/day divided in two doses. For a child of approximately 16 kg, suspend and have the child drink one-200 mg tablet in water every 12 hours. The child must drink the entire volume of suspended drug.

TABLE 1.
NUMBER OF AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS FOR ORAL SUSPENSION TO BE GIVEN TO ACHIEVE RECOMMENDED DOSES

RECOMMENDED DOSAGE OF AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS FOR ORAL SUSPENSION	CHILD'S WEIGHT (KG)	NUMBER OF TABLETS FOR SUSPENSION PER DOSE
NEONATES		
15 mg/kg, every 12 hours[3] (30 mg/kg/day)	13	One-200 mg tablet
CHILDREN 3 MONTHS AND OLDER		
22.5 mg/kg, every 12 hours (45 mg/kg/day)	9	One-200 mg tablet
	18	One-400 mg tablet
12.5 mg/kg, every 12 hours (25 mg/kg/day)	16	One-200 mg tablet
	32	One-400 mg tablet
ADULTS AND CHILDREN 3 MONTHS AND OLDER		
45 mg/kg, every 12 hours (90 mg/kg/day)	13	One-600 mg tablet
	26	Two-600 mg tablets

The label for Augmentin ES-600™ Powder for Oral Suspension specifies doses for the pediatric population from ages 3 months and older:

> Children 3 months and older: The recommended dose is 90 mg/kg/day divided into two doses.

The planned labeling for Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension (600 mg amoxicillin and 42.9 mg clavulanate potassium) will be very similar in providing dose information for the allowable weight groups:

> Children 3 months and older: Administer 90 mg/kg/day divided in two doses. For a child of approximately 13 kg, suspend and have the child drink one-600 mg tablet in water every 12 hours (see Table 1 above). The child must drink the entire volume of suspended drug.

Further, a bioequivalence study is planned comparing the Reference Listed Drug with Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension and a product demonstrated to be bioequivalent in adults is accepted to be bioequivalent in a pediatric population. Therefore, additional studies would be redundant and unnecessary.

The planned bioequivalence study will compare Augmentin ES-600™ Powder for Oral Suspension (600 mg amoxicillin and 42.9 mg clavulanate potassium/5 mL) with Amoxicillin

[3] Highly unlikely that this age group will receive the proposed product because of normal neonate and infant body weight ranges.

and Clavulanate Potassium Tablets for Oral Suspension (600 mg amoxicillin and 42.9 mg clavulanate potassium) in adult volunteers. The petitioner believes that the bioequivalence study conducted on adults should be adequate to demonstrate bioequivalence in children.

According to the approved labeling, Augmentin®/Augmentin ES-600™ Powder for Oral Suspension[1] is recommended for use in pediatric patients from neonatal age and older. The petitioner's product, in line with the Reference Listed Drug, is also indicated for use in pediatric patients 3 months of age and older within the correct weight range for dosing. Based on the limited pediatric patient population, the petitioner believes that there will not be substantial use of the product in pediatric patients, and therefore does not warrant a pediatric study.

For the reasons stated above and consistent with the provisions of the Pediatric Research Equity Act of 2003, the petitioner respectfully requests that this waiver be granted.

Sincerely,

Nick Fleischer @

Nicholas M. Fleischer, R.Ph., Ph.D.
Director of Biopharmaceutics
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Enclosure

cc Gary Buehler, Director, Office of Generic Drugs